

Case Report

Psychosis from subthalamic nucleus deep brain stimulator lesion effect

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Abstract

Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) in particular is highly effective in relieving symptoms of Parkinson's disease (PD). However, it can also have marked psychiatric side effects, including delirium, mania, and psychosis. The etiologies of those effects are not well-understood, and both surgeons and consulting psychiatrists are in need of treatment strategies.

Case Description: Two patients with young onset of PD and without significant prior psychiatric problems presented for bilateral STN DBS when medications became ineffective. Both had uneventful operative courses but developed florid psychosis 1-2 weeks later, before stimulator activation. Neither showed signs of delirium, but both required hospitalization, and one required treatment with a first-generation antipsychotic drug. Use of that drug did not worsen PD symptoms, contrary to usual expectations.

Conclusion: These cases describe a previously unreported post-DBS syndrome in which local tissue reaction to lead implantation produces psychosis even without electrical stimulation of subcortical circuits. The lesion effect also appears to have anti-Parkinsonian effects that may allow the safe use of otherwise contraindicated medications. These cases have implications for management of PD DBS patients postoperatively, and may also be relevant as DBS is further used in other brain regions to treat behavioral disorders.

Key Words: Deep brain stimulation, neuromodulation, neurostimulation, Parkinson's disease, psychosis, subthalamic nucleus

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INTRODUCTION

Deep brain stimulation (DBS) improves neurologic and psychiatric symptoms by altering the tonic activity of subcortical circuits. While the precise mechanism of action remains unclear,^[17] high-frequency stimulation seems to simulate a shapeable lesion of the targeted

area. The majority of procedures currently performed are for idiopathic Parkinson's disease (PD), with the globus pallidus and subthalamic nucleus (STN) as common stimulation targets. This raises concerns for psychiatric complications, as STN is involved in limbic/emotional regulation.^[25] Reported complications of STN DBS have included transient manias and/or delirium,^[4,12,16,19,20,21,32]

persistent hallucinations and long-term mood dysregulation, and suicides.^[6,15,25,26,29] All previously reported psychiatric complications (except delirium) occurred only after onset of chronic brain stimulation.

We treated two patients who developed agitated psychosis (without mood or delirium symptoms) after bilateral STN DBS implantation. These psychoses occurred before stimulation, and we hypothesize that they arise from tissue response to electrodes in the STN. In addition to representing an STN DBS complication not previously described, these cases presented pharmacologic surprises. By comparing the management of two similar patients treated a year apart, we hope to provide guidance for DBS teams faced with this issue in future.

CASE REPORT

Patient A

A 47-year-old, right-handed, Caucasian male presented for STN DBS 10.5 years after his initial PD diagnosis. He had no prior psychiatric history except depression that began as a symptom of PD. A pramipexole trial to 2.5 mg total daily dose had produced impulsivity, hypersexuality, jealousy, and compulsive gambling, which remitted after he stopped. He was a nonuser of tobacco, ethanol, or illicit drugs. He had no family history of major mental illness.

By the time of surgery, he had severe bilateral rigidity, painful dystonias, and persistent neck extension. His United Parkinson's Disease Rating Scale (UPDRS) Part III motor score before surgery was 48 off medication and 13 on medication. Medications prior to surgery were amantadine, carbidopa-levodopa, entacapone, selegiline, baclofen, escitalopram, and calcium carbonate. The levodopa equivalent dose (LED) was 3140 mg daily, calculated as per Tomlinson *et al.*^[27] He had substantial "wearing off" and disability even with this aggressive regimen. The risks and benefits of DBS were carefully weighed in Mr. A given his history of psychiatric complications. However, given his high level of disability and distress, the potential benefits were felt to have more weight. With his history of impulsivity with pramipexole, STN was selected as the DBS target to allow substantial reduction of his medication dosage.

Bilateral placement of STN-targeted DBS used initial coordinates chosen using a compromise between standard anterior commissure-posterior commissure (AC-PC) based coordinates, and coordinates relative to the borders of the red nucleus. Final planned coordinates were [x, y, z]: [-11.6, -3.5, -4.1 mm] on the left and [11.9, -3.6, -3.9 mm] on the right, relative to mid-commissural point and the AC-PC plane. Coordinates are not whole numbers as they reflect the rounding of corresponding Leksell frame-based

coordinates to the nearest half-millimeter. Two guide cannulas were passed on each side. On the right, STN-like cellular activity was recorded from 2.6 mm above to 1.8 mm below the target, with modulation of firing rates with passive joint movement of the upper and lower extremity. Macrostimulation through a DBS electrode placed with its distal contact at 1.5 mm below target improved rigidity. On the left, STN activity spanned 3.8 mm above to 1.7 mm below target, with modulation with passive movement of right upper extremity. On this side also, the DBS lead was placed with distal contact 1.5 mm below target, with rigidity improvement during stimulation. Stimulation on both sides evoked transient paresthesias without dysarthrias at 1.5 V on the right and 4 V on the left. Intraoperative DBS positioning was confirmed using postoperative extended Hounsfield unit (EHU) computed tomography (CT) co-registered to preoperative magnetic resonance imaging (MRI) in standardized coordinates.^[10] This technique utilized both normalized mutual information (NMI) co-registration and manual paired-point anatomical registration methods to ensure there were no significant measurement errors due to brain shift. Whereas the NMI technique may favor co-registration of skull anatomy and thus not account for brain shift, the paired point registration provided verification by emphasizing anatomical structures such as the temporal horns, tectal plate, and trigeminal root entry. Atlas registration of final coordinates^[18] is shown in [Figure 1], with EHU CT-MRI imaging in [Figure 2] and coordinates for both patients in [Table 1].

Mr. A reported no major physical or mental symptoms postoperatively and underwent generator placement 1 week later without incident. Five days after generator placement (12 days post-DBS), he reported a robust microlesion effect, and reduced his medications to a LED of 1048 mg. He had no noticeable motoric side effects from this substantial decrease. Over the next 3 days, he became increasingly anxious, paranoid, and delusional, presenting twice to the emergency room (ER). Head CT, basic laboratory studies, and a lumbar puncture were all unremarkable. Amantadine, selegiline, and escitalopram were stopped, baclofen continued, and agitation treated with quetiapine. However, he continued to decline, making sexual comments toward nurses and refusing food. He remained fully oriented without hallucinations. Vital signs were normal.

Three days after admission, his agitation progressed to requiring physical restraints after he attempted violence against staff. He then refused all medications. After consideration of available options, he received 7.5 mg of intramuscular olanzapine against his will, which calmed him enough to engage in care and accept oral medications. Psychotic symptoms, including agitation, possible hallucinations, and impulsivity, persisted for

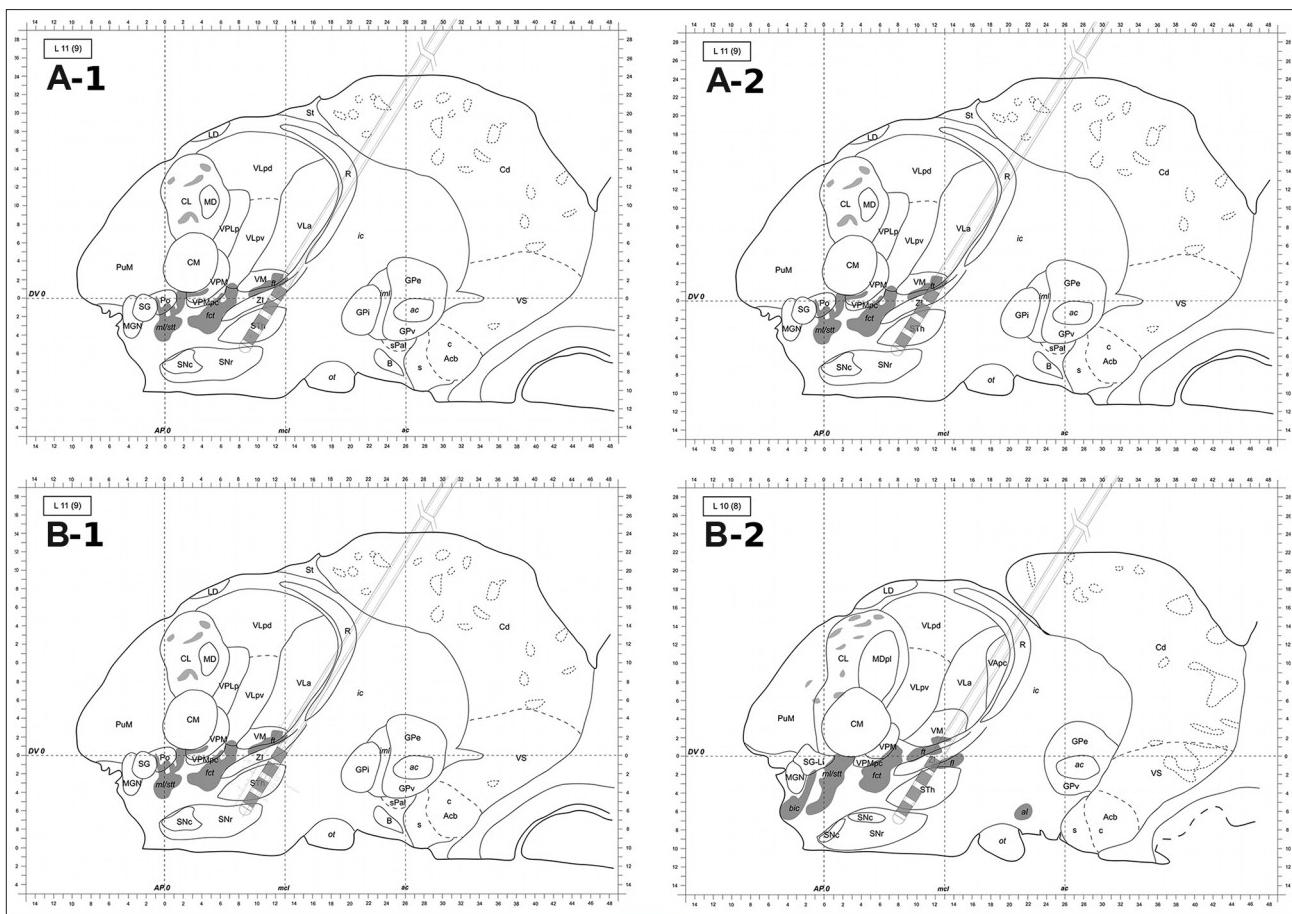


Figure 1: Overlay of final DBS lead positions (as calculated from postoperative EHU CT) on stereotactic atlas plates. A and B designate patients A and B whereas 1 and 2 designate left and right hemispheres, respectively. Notably, all four leads pass fully though STN into the substantia nigra (SNr), implying that the postoperative lesion effect could include the effects of SNr tissue destruction. Plates are reproduced with permission from Morel 2007; patient A is overlaid on figure 4-31 (lateral 11 mm), and B on 4-31 (lateral 10 mm) for left and 4-30 (lateral 10 mm) for right

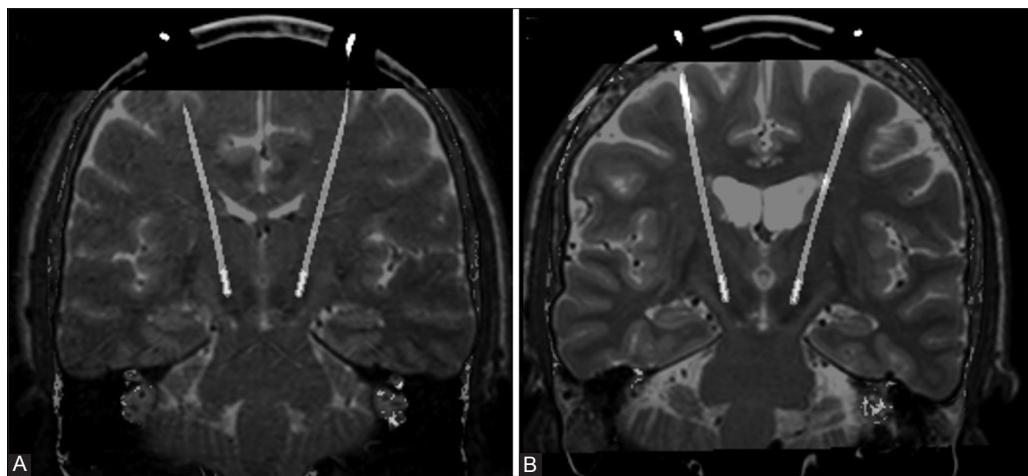


Figure 2: Co-registration of coronal reconstruction from preoperative MRI with postoperative EHU CT and automatic identification of DBS leads, revealing the final location of DBS implants in patients A and B

at least a week more, up to POD 21. He did accept olanzapine 15 mg orally daily, plus his carbidopa-levodopa and entacapone. Starting on POD 22, he became apologetic for his behavioral outbursts, but retained

memory for his actions. He continued to experience vivid dreams, but not waking hallucinations. He remained in the hospital on a psychiatric commitment until 15 days' hospitalization. Toward the end of this, he was

cooperative with care, oriented, still apologetic, and entirely appropriate and coherent in his thoughts and speech.

He left the hospital on escitalopram (restarted), entacapone and carbidopa-levodopa (reduced dosing), and olanzapine 5 mg BID, with no signs of psychosis. By 3 months postdischarge, his only medications were carbidopa-levodopa, entacapone, and escitalopram (LED of 1064 mg). Stimulator programming/activation at POD 52 [settings in Table 2] did not cause new psychiatric symptoms, and he has remained psychiatrically stable for over 3 years. His pain and motor function have improved and he has expressed satisfaction with the surgery.

Patient B

A 47-year-old Caucasian man presented for STN DBS 5 years after his PD diagnosis. He reported no other medical problems. **He had no prior psychiatric problems or family history of major mental illness, had quit tobacco**

over 20 years earlier, and used minimal alcohol. Like Mr. A, Mr. B had psychiatric side effects from pramipexole at doses above 4.5 mg daily. His personality had become more outgoing, he made inappropriate sexual comments, and he had a gambling addiction that prevented him from managing his own money. Despite these problems, he had experienced sufficient benefit that he had chosen to continue pramipexole. Neuropsychiatric testing 1 month before surgery was remarkable only for “minimal signs of depression” and nonspecific cognitive impairments suspected to be lifelong.

Mr. B presented for surgery early because PD was impairing his ability to work as a heavy equipment operator. His UPDRS Part III motor score 1 month before surgery was 37 off medication and 14 on medication. Prior to surgery, he was taking carbidopa-levodopa, clonazepam (for sleep), pramipexole, selegiline, and quetiapine (25 mg, for vivid dreams). The LED was 1600 mg.

Table 1: Planned and final (computed from EHU CT co-registered to preoperative MRI) electrode localizations relative to the AC-PC plane, in [x y z] format, along with Euclidean distance between planned and actual placement. All distances are in millimeters.

| Patient A | | | | | |
|-------------------|-------------------|----------|------------------|------------------|----------|
| Left | | | Right | | |
| Plan | Actual | Distance | Plan | Actual | Distance |
| -11.6, -3.5, -4.1 | -11.4, -3.8, -4.2 | 0.37 | 11.9, -3.6, -3.9 | 11.7, -4.4, 4.2 | 8.14 |
| | -11.8, -2.8, -2.6 | 1.67 | | 12.2, -3.5, -2.6 | 1.34 |
| | -12.2, -1.8, -0.9 | 3.67 | | 12.6, -2.5, -1.0 | 3.18 |
| | -12.7, -0.8, 0.7 | 5.62 | | 13.1, -1.6, 0.6 | 5.07 |
| Patient B | | | | | |
| Left | | | Right | | |
| Plan | Actual | Distance | Plan | Actual | Distance |
| -11.4, -2.8, -3.3 | -12.4, -3.8, -4.8 | 2.06 | 11.6, -2., -3.5 | 9.6, -4.1, -5.1 | 3.31 |
| | -12.9, -2.8, -3.2 | 1.50 | | 10, -3.2, -3.9 | 2.04 |
| | -13.3, -1.7, -1.5 | 2.84 | | 10.4, -2.3, -2.5 | 1.59 |
| | -13.8, -0.6, 0.1 | 4.71 | | 10.8, -1.4, -1.2 | 2.51 |

Table 2: Initial and most recent programming settings for each patient’s deep brain stimulation. Settings have shifted more on the right than on the left for both patients, consistent with worse Parkinsonism on the nondominant side. POD, postoperative day; POM, postoperative month

| Patient | Lead | Amplitude (V) | Pulsewidth (μs) | Rate (Hz) | (+) Contact | (-) Contact |
|----------|------|---------------|-----------------|-----------|-------------|-------------|
| A POD 52 | L | 1.0 | 60 | 135 | Case | 2 |
| | R | 1.0 | 60 | 135 | Case | 2 |
| A POM 31 | L | 3.2 | 60 | 135 | Case | 2 |
| | R | 3.5 | 90 | 135 | Case | 2 |
| B POD 55 | L | 1.0 | 60 | 130 | 3 | 2 |
| | R | 1.0 | 60 | 130 | 2 | 1 |
| B POM 21 | L | 2.3 | 60 | 130 | Case | 2 |
| | R | 3.5 | 90 | 185 | 2 | 1 |

POD: Postoperative day, POM: Postoperative month

Target AC-PC based coordinates for Mr. B were [x, y, z]: [-11.4, -2.8, -3.3 mm] on the left and [11.6, -2.7, -3.5 mm] on the right. STN-like activity on the left spanned 1.9 mm above to 1.7 mm below target, with arm movement related cells within 1 mm of target. Two guide cannulas were passed on the left, and three on the right. On the right, few cells were noted along the entire trajectory, although STN-like activity could be found from 0.24 mm above to 2.8 mm below target. One neuron that modulated its firing rate with hand grip was found at 0.24 mm above target. On both sides, Mr. B's rigidity improved substantially simply by electrode passage, and it was difficult to assess for further response to stimulation. Electrodes were placed with their distal contacts at 2.5 mm below target on both sides, as shown in Figures 1 and 2. Transient paresthesias were elicitable at 2.6 V on the left, and as little as 2 V on the right during macrostimulation testing with the DBS electrode.

Postoperatively, he was more somnolent than expected. EHU head CT done for lead placement verification^[11] showed a 3 × 9 mm right thalamic hyperdensity. After overnight observation, he was fully alert and oriented, and repeat CT showed no change in the thalamic hyperdensity. He discharged with only some right hand paresthesias. 1 week later, he reported some worsened dyskinesias and left upper extremity tremor, but no psychiatric symptoms. He had been able to slightly decrease his levodopa-carbidopa regimen, to an LED of 1525 mg.

Repeat CT at 13 days postelectrode placement showed hemorrhage resolution, and he underwent generator placement the next day. His wife reported that since his 1-week checkup, Mr. B had become more impulsive and his gambling addiction had worsened. These symptoms were not attributed to his DBS, and he did not show any delirium or complications after generator placement, leading to discharge the same day.

Two days later (15 days postelectrode placement), on an international trip, he developed hypoverbalism and a sense of near-continuous *déjà vu*. Selegiline was stopped. On return, when visiting his neurologist for evaluation, he became frightened and would not enter the appointment. By 19 days postelectrode placement, he was mostly nonverbal, but would have periods of hyperverbalism and agitation. He ran away from our university ER when brought for evaluation, and had to be tricked into taking a dose of quetiapine and then rapidly driven back to the ER. He would not speak to the evaluating residents or remain in his room, although he did follow commands and comply with medical evaluation.

Mr. B's ER workup, including basic laboratory panels and another head CT (but not lumbar puncture) was unrevealing. He was admitted, and required a sitter to

prevent him from leaving, but did not need physical restraint. Pramipexole was stopped, carbidopa-levodopa continued, clonazepam supplemented with lorazepam, and quetiapine repeatedly increased. He worsened, disclosing paranoid and grandiose delusions, although he remained fully oriented with an intact sensorium.

Mr. B markedly decompensated on the third hospital day (POD 22), when he developed visual hallucinations. He struggled against restraints so forcefully as to damage his hospital bed. At his most acute point, he had received a total of 150 mg quetiapine and 1.5 mg of IM lorazepam without effect, and refused further oral medication. IM olanzapine was considered unsafe due to the potential hypotensive interaction with lorazepam. After extensive deliberation and conclusion that the need to control an acute physical emergency outweighed the risks, 0.5 mg of haloperidol was given IV, and repeated roughly an hour later. This controlled his acute agitated state, and produced very minimal cogwheeling at wrists and ankles. He remained in restraints overnight, accepted more oral quetiapine at his wife's urging, and became calmer. He remained on his outpatient carbidopa-levodopa dose (1350 mg total) throughout these events.

By the following day, Mr. B no longer reported delusions or hallucinations and had calmed substantially. Over days 5 through 8 of his hospitalization, restraints were reduced, carbidopa-levodopa eliminated, and quetiapine given for agitation. He remained oriented, albeit concrete and without insight into his situation. He continued to have slight cogwheeling on passive extremity motion, but otherwise was without PD symptoms. At discharge on POD 27, he was in good behavioral control and his only medication was quetiapine, 350 mg daily.

Mr. B's DBS was activated and programmed at POD 55, and was uncomplicated [settings in Table 2]. He returned to work and slowly tapered off quetiapine. He continues to show minimal PD symptoms at 2 years postsurgery, and has returned to both independent driving and his job operating heavy machinery.

DISCUSSION

These two patients, both of similar age and with minimal prior psychiatric history, developed a psychotic syndrome roughly 2 weeks after DBS electrode implantation, before their stimulators were active. Our first consideration in each case was delirium, but that syndrome requires disorientation and a waxing-waning course. Delirium has been reported in multiple large DBS case series, but generally in the immediate postoperative period.^[20] Mania is a known side effect of STN DBS, but has always been reported in the context of stimulation, presumably by activation of limbic efferents from the STN.^[12,20] For our patients, we hypothesize that contributing factors to their psychoses included underlying vulnerability

of STN-related circuits, younger than usual age at surgery, and the tissue injury response (lesion effect) from electrode placement. While the tissue response to DBS is not easily studied in humans, numerous rodent studies have shown a complex response that transforms from acute to chronic over 2-6 weeks.^[9,30] This fits the time course of the symptoms we observed, and is circumstantial evidence for a hypothesis that increasing local tissue response to the DBS lead was responsible for the psychosis. Both men showed a rapid relief of PD signs from electrode placement without passage of current, suggesting a particularly vigorous sub-acute lesion effect. This was particularly evident in Mr. A, whose LED dropped by roughly 66% postoperatively, although the motor improvement preceded development of psychosis by a few days. This marked dopaminergic withdrawal is also intriguing, but would be unlikely to contribute to psychosis, given that dopamine is, in a broad sense, psychotogenic. The second patient also had a millimeter-scale thalamic hemorrhage, although the resolution of this bleeding before symptom onset argues against its role in the psychosis.

Both patients experienced impulsivity and abnormal behaviors with pramipexole, suggesting an underlying vulnerability of their mesolimbic pathways. This may have been especially relevant for Mr. B, whose subcortical pathways had already been stressed by a thalamic hemorrhage. Both were also younger than the average PD patient who undergoes DBS, which we speculate could lead to stronger limbic connections from the STN and more vulnerability to abnormal circuit activity resulting from the lesion effect. The ventral STN in particular, and the substantia nigra (SN) below it, have been associated with limbic side effects in small studies.^[2,5,8,28] Both patients had DBS leads placed within and injuring those zones, although the same is true of many STN DBS patients who do not develop psychosis. Age may be particularly important in this interaction. SN is known to store dopamine,^[3,14] and injury of a younger and less degenerated SN could lead to excess dopamine release throughout the brain, predisposing patients to psychosis (particularly when dopaminergic medications are continued.)

Finally, some experienced practitioners have opined that bilateral STN DBS carries a higher risk of psychiatric complications and that patients should first have unilateral DBS contralateral to the more-impaired limbs.^[1] In contrast, two case series representing 42 patients did not find changes in mood or anxiety scales when patients converted from unilateral to bilateral STN DBS.^[22,23] Bilateral placement on a single day is not entirely equivalent to staged bilateral STN DBS, but the finding that the presence of bilateral stimulators does not *per se* carry an increased weight of psychiatric complications argues against a role for bilateral surgery in the etiology of these two cases.

In both cases, management was complicated by the risk of Parkinsonian symptoms associated with antipsychotic use (extrapyramidal symptoms, EPS). Clozapine is often recommended for chronic psychosis associated with PD,^[24,31] but is not readily available in emergencies. More importantly, severely agitated patients often refuse oral medications. Olanzapine and haloperidol, two commonly used antipsychotics with parenteral forms, are generally considered contraindicated in PD as they may worsen motor symptoms.^[7] We nevertheless were forced to resort to these medications when the acute behavioral emergency shifted the risk-benefit calculation. We were surprised to find no substantial motor complications, even from haloperidol. We attribute this to the strong anti-Parkinsonian properties of the microlesion effects seen in these patients, which would protect against drug-induced Parkinsonism much the same way that active DBS could; this cannot be conclusively separated from the hypermotoric effects of agitation.

A key finding in these cases is thus that a brief course of high-potency antipsychotics may be safe in the acutely agitated DBS patient in the presence of substantial lesion effect, although this may be limited to younger patients who retain some dopaminergic reserve. Both patients also continued selegiline preoperatively and remained on carbidopa-levodopa as their psychosis escalated. This decision was made out of fear of worsening PD and/or triggering neuroleptic malignant syndrome,^[13] but in retrospect, more aggressive reduction of dopaminergic tone may have prevented the worst of their psychosis, avoiding distress to patients, family, and staff. Here again, the lesion effect would compensate for loss of exogenous dopamine.

CONCLUSION

Limbic hyperactivation leading to mania and psychosis has been reported as a consequence of electrical STN stimulation, but before now has not been described to arise directly from injury of STN and surrounding structures by a DBS lead. In addition to suggesting new mechanisms for this complication, these cases demonstrate that in this unique situation it may be safe to use high-potency antidopaminergic medications that would normally be contraindicated in PD. Our hypothesis is that the same tissue lesion that causes psychosis also protects against Parkinsonism. They may also suggest that dopaminergic medications such as selegiline (which has psychoactive metabolites) could be more aggressively reduced preoperatively in younger PD patients with evidence of mesolimbic sensitivity. As more DBS is performed for both PD and psychiatric indications, cases such as these will increase in frequency. Psychiatric complications of DBS are sometimes reported as part of long-term follow up studies, but none of the reports we reviewed gave details of the events or management,

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or details on precise placement of leads. It would be very helpful for those centers with large DBS registries to publish some larger case series to better guide future treatment.

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